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10/560,653	11/20/2006	David B. Weiner	130694.02201	2032

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EXAMINER	
LI, BAO Q	
ART UNIT	PAPER NUMBER
1648	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/560,653	WEINER ET AL.	
	Examiner	Art Unit	
	BAO LI	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 September 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-8,10-15,17-19 and 22-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2, 4-8, 10-15 and 17-19, 22-32 in the scope of OX40* is/are rejected.

7)☒ Claim(s) *1* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Summery

The amendment and response filed on March 23, 2009 have been acknowledged. Claims 7 and 15 have been amended. Claims 3, 9, 16, 20-21 have been canceled. New claims 27-32 have been added.

In summery, claims 1-2, 4-8, 10-15 and 17-19, 22-32 are pending and considered within the elected scope of Ox40.

Examiner's note: Upon further considering the pending claims, a reasonable broadest interpretation of the scope for claims 7, 10, 23, 28, 31, 15, 17, 24, 29 and 32 are still explained as two nucleic acid sequences carried by either two separate expression vectors/plasmids or one expression vector/plasmid as claim 8 cited.

Claim Rejections - 35 USC § 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. The rejection of claims 1, 4-5, 13, 22 under 35 U.S.C. 102 (b) as being anticipated by US Patent No. 6,017,735A to O'Hare et al . has been moot in view of a new ground rejection set forth below.

3. New ground rejections:

4. Claims 7, 10-12, 14, 15, 17, 23-29, 31, 32 are rejected under 35 U.S.C. 102 (b) as being anticipated by US Patent No.6, 344,445B1 to Boursnell et al.

5. Boursnell et al. teach a method for making a pharmaceutical composition (column 5) using an attenuated or mutated HSV1 or HSV2 as a expression vector that carries a nucleic acid sequence encoding an immunomodulatory sequence of OX40, wherein the HSV1 or HSV2 has gH gene deletion (columns 5-6 and 15-16), the antigen can be pathogenic virus related viral antigen as well as a cancer antigen from EBV or HPV in addition to the HSV itself inherently. One of immunomodulatory proteins can be OX40 (See column 14). While the reference does not

explicitly teach the composition comprising such viral vector as an injectable formulation, it inherently teaches that the composition is an injectable pharmaceutical composition suitable for transducing normal or malignant human hemopoietic progenitor cells or tumor cells as an liquid formulation (column 14), because the powder of a viral vector is not applicable for transducing the hemopoietic cells or tumor cells in vitro, in vivo or ex vivo without any pharmaceutical accepted carrier. Therefore, the composition of said HSV2 replication defective or mutant vector comprising a heterologous nucleic acid sequence encoding the OX40 and inherently the endogenous viral sequence encoding HSV2gD, which are separated located in the viral vector construct, meet the limitation of the rejected claims. The cited reference anticipates the rejected claims.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1-2, 4-8, 10-15 and 17-19, 22-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 6,344,445B1 to Boursnell et al. and further in view of Rosen et al. (US Patent Application 2002/0044941A1) for claims 1-2, 4-6, 13, 14, 22, 27, 30 and Hodge et al. (JNCI 2000, Vol. 92, No. 15, pp. 1228-1239) for claims 18-19.

8. Boursnell et al. teach a method for making a pharmaceutical composition (column 5) using an attenuated or mutated HSV1 or HSV2 as a expression vector that carries a nucleic acid sequence encoding an immunomodulatory sequence of OX40, wherein the HSV1 or HSV2 has gH gene deletion (columns 5-6 and 15-16), the antigen can be pathogenic virus related viral antigen as well as a cancer antigen from EBV or HPV in addition to the HSV itself inherently. One of immunomodulatory proteins can be OX40 (See column 14). While the reference does not explicitly teach the composition comprising such viral vector as an injectable formulation, it inherently teaches that the composition is an injectable pharmaceutical composition suitable for

transducing normal or malignant human hemopoietic progenitor cells or tumor cells as an liquid formulation (column 14), because the powder of a viral vector is not applicable for transducing the hemopoietic cells or tumor cells in vitro, in vivo or ex vivo without any pharmaceutical accepted carrier. Therefore, the composition of said HSV2 replication defective or mutant vector comprising a heterologous nucleic acid sequence encoding the OX40 and inherently the endogenous viral sequence encoding HSV2gD, which are separated located in the viral vector construct, meet the limitation of the rejected claims. Boursnell et al. do not teach using vaccine viral vector or using two plasmids for carrying one nucleic acid sequence encoding an antigen and another encoding OX40 protein in separate expression plasmids or expression vectors.

9. Hodge et al. teach a method for constructing a flowpoxvirus viral vector (rF-TRICOM) or vaccine virus vector (rV-TRICOM) to express more than one co-stimulatory molecule that successfully transducing/infecting antigen presenting cells of dentritic cells as well as activating T cells. They concluded that the ability of dendritic cells to activate both naive and effector T cells *in vitro* and *in vivo* can be enhanced with the use of poxvirus vectors that potentiate the hyperexpression of a triad of costimulatory molecules. Use of either rF-TRICOM or rV-TRICOM vectors significantly improved the efficacy of dendritic cells in priming specific immune responses. These studies have implications in vaccine strategies for both cancer and infectious diseases (See abstract and detail in Materials and Methods section as well as Figs. 1-4).

10. Rosen et al. teach in [0920-0939] a therapeutic composition and a method of using the same to treat disease or disorders particularly a lung caner. In particular, Rosen et al. teach that the method can be processed by administering a composition comprising a polynucleotide encoding an antigen isolated from a lung cancer or any tumor associated antigen [Abstract and 0746-0750]. Rosen et al. teach that said plynucleotide carried by an expression vector as a therapeutic agent can be administrated with a member of TNF family immunomodulatory molecules, such as OX40 [0939]. Rosen et al. also teach that the composition can be formulated for parenteral, intravenous, intramuscular and intraarticular injection administration [0923]. Rosen et al. do not teach explicitly that the OX40 can be administrated as a DNA molecule.

11. Therefore, it would have been obvious for a person ordinarily skilled in the art to be motivated to adapting all teachings by Roursnell, Rosen and Hodge et al for making an

immunogenic composition comprising one or more expression vectors or plasmids comprising one nucleic acid encoding an immunogenic antigen in combination with another nucleic acid encoding the immunomodulatory molecule such as OX40 either in a separate expression vector or same expression vector to produce a better immune response when they are used together with an expected result as taught shown by Boursnell, Hodge and Rosen et al. et al. Hence, the claimed invention as a whole is prima facie obvious absence unexpected results.

12. Claims 7-8, 10, 15, 17 23, 24, 28, 29, 31 and 32 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over US Patent No. 6,017,735A to O'Hare et al.

13. Upon further considering the pending claims, a reasonable broadest interpretation for the scope of claims 7-8, 10, 23, 28, 31, 15, 17, 24, 29 and 32 can still be explained as two nucleic acid sequences carried on by one nucleic acid molecule carried by one plasmid as claim 8 cited. Therefore, they are still anticipated or alternative as obvious to O'Hare' reference set forth below:

14. O'Hare et al. teach a polynucleotide expression vector or a plasmid comprising two separate coding sequences in one nucleic acid expression construct carried by one expression vector or plasmid. The first one of the nucleic acid sequence encodes an antigenic protein selected from a pathogenic virus, such as Hepatitis B virus or a tumor associated antigen optionally fused or coupled to HSV antigenic translocator protein PV20 and the second nucleic acid sequence encodes an immunomodulatory protein including OX40 (See claims 1 and column 12). To this context, the polynucleotide construct of the expression vector or plasmid comprising these two separate coding sequences taught by O'Hare et al. meets the limitations of broad scope of claims 7-8, 10, 23, 28, 31, 15, 17, 24, 29 and 32 that still not limited to two separate nucleic acid sequences presented or carried by two individual plasmids or expression vectors.

15. While O'Hare et al. do not explicitly teach the polynucleotide sequence is contained in a composition, any person ordinarily skilled in the art would understand that such polynucleotide construct is implicitly taught or inherently presented as a composition regardless a carrier buffer packed in a container.

16. Or alternative, it would have been obvious for any person ordinarily skilled in the art to place said polynucleotide construct in any kind of buffer with expected success. Hence, the claimed invention as a whole is prima facie obvious absence unexpected results.

17.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

18. The rejection of claims 1-2, 4-8, 10-15 and 17-19, 22-26 are maintained under 35 U.S.C. 112, first paragraph. It should be clear what the fragment functionally means.

19. Applicants' argument has been respectfully considered; however it is not persuasive, because the definition of the fragment only give a concept for cited language that meets the requirement of 112 2nd, but the specification still lacks a description what the fragment that Applicants is in possession for the claimed composition. The definition fails to the test of written description under 112 1st paragraphs, i.e. To determine whether Applicants have a possession for the claimed subject or the claimed subject matter lacks of a written description, it is considered based on 1). Full coverage of the claimed scope of invention; 2). Whether applicant provides sufficient support to support the full scope of the invention and 3). Whether one skilled in the art would recognize that the applicant was in possession of the claimed invention as a whole at the time of filing according to the disclosure of the entire application. This should include the following aspects of the considerations: a. Actual reduction to practice; b. Disclosure of drawings or structural chemical formulas; c. Sufficient relevant identifying characteristics including i). Complete structure, ii). Partial structure; iii). Physical and/or chemical properties and iv). Functional characteristics when coupled with a known or disclosed correlation between function and structure; d. Method of making the claimed invention; e. Level of skill and knowledge in the art; f. Predictability in the art.

20. For a claim drawn to a genus, consideration needs also focusing on each of the above factors to determine whether there is disclosure of a representative number of species which would lead one skilled in the art to conclude that applicant was in possession of the claimed

invention. The number of species required to represent a genus will vary, depending on the level of skill and knowledge in the art and the variability among the claimed genus. For instance, fewer species will be required where the skill and knowledge in the art is high, and more species will be required where the claimed genus is highly variable. Based on the disclosure of the specification, which lacks of evidence of reduction to the practice, lacks of description of any other species of the claimed virus or nucleotide sequence, lacks of the description of the structure, function as well as the relationship between the structure and function, it is concluded that one skilled in the art would recognize that the applicant was in possession of the claimed invention as a whole at the time of filing according to the disclosure of the entire application, especially the claimed invention belongs to a very unpredictable filed.

21. According to the specification, the field is very unpredictable (Please see the enablement rejection below). Applicants describe that the full length OX having an activity to enhance the immune response, but it does not describe any fragment having such activity, and which fragment of the OX40 can produce such activity.

22. A determination as to whether one skilled in the art would recognize that the applicants were in possession of the claimed invention as a whole at the time of filing, the following analyses are conducted and considered: a). Actual reduction to practice; b). Disclosure of drawings or structural chemical formulas; c). Sufficient relevant identifying characteristics, which include: (i). Complete structure; (ii). Partial structure, (iii). Physical and/or chemical properties; (iv). Functional characteristics when coupled with a known or disclosed correlation between function and structure; d). Method of making the claimed invention; e). Level of skill and knowledge in the art; f). Predictability in the art.

23. In the instant case, for all disclosure considered including the drawing, no any fragments have been presented. which would lead one skilled in the art to conclude that applicant was not in possession of the claimed invention.

24. MPEP § 2163.02 states, "[a] n objective standard for determining compliance with the written description requirement is "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed' ". The courts have decided: The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of

the filing date sought, he or she was in possession of the invention. The claimed fragment in the composition does not meet the written description and enablement provision of 35 U.S.C. 112, first paragraph. Wherein the enablement rejection is further explained below:

25. **(New ground of rejection).** Claims 15, 17, 18, 19, 24, 29, 32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for having an immunogenic composition comprising an expression vector or plasmid carrying a nucleic acid molecule encoded by two separate coding sequences of an antigen, preferably, a pathogenic viral antigen of Herps virus glycoprotein D and the immunomodulatory protein of OX40 or its fragment thereof, does not reasonably provide enablement for having a vaccine comprising said expression vector or plasmid. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

26. The test of scope of the enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation (See United States v. Theketronic Inc., 8USPQ2d 1217 (fed Cir. 1988). Whether undue experimentation is required is not based upon a single factor but rather a conclusion reached by weighting many factors. Theses factors were outlined in Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in re Wands, 8USPQ2d 1400 (Fed. Cir. 1988). These factors include the following: 1). The nature of invention, 2). The scope of claims, 3). State of art, 4). Unpredictability of the art, 5). The working example and guidance provided by the specification, 6). The level of Skill in the art, and 7). The amount of the work required to fulfill the scope of the claims encompassed.

27. In the instant case, the claimed invention is an immunogenic composition made from one or two nucleic acid constructs carried by one or two separate expression vectors or plasmids, wherein the two coding sequences are any or all kinds of antigens including tumor or a pathogenic viral antigen, preferably, the herpes simplex virus glycoprotein2 D (HSV2gD) and another is the immunomodulatory molecule OX40.Moreover, the claimed subject matter is also broadly directed to a method using any or all fragment of OX40 and an antigen as a vaccine composition.

28. The state of art teaches that several members of the TNFR superfamily, including OX40 (CD134), 4-1BB (CD137), and CD27 provide critical costimulatory signals that promote T cell survival and differentiation in vivo. Although several studies have demonstrated that OX40 engagement can enhance CD4 T cell responses, the mechanisms by which OX40-mediated signals augment CD8 T cell responses are still unclear as evidenced by Redmond et al. (J. Immunol. 2007, Vol. 179, pp. 7244-7253). Moreover, the state of art also teaches that a single amino acid change could completely alter the biological activity of the biological active molecule as evidenced by Lederman et al. (Molecule Immunology 1991, Vol. 28, No. 11, pp. 1171-1181).

29. It is well know in the art that many pathogenic viruses including HSV infection is a latent infection and no vaccine is available for protecting human or animal infection. Therefore, it is unpredictable for making a vaccine using the OX40 in combination with any antigen. A person skilled in the art would need to do undue experimentation to fulfill the broad scope of claims read on a protective immune response. Applicants do not provide any example showing that the plasmid encoding any antigen in combination with another plasmid encoding OX40 can be used as a vaccine. The enhancing immune response to HIV eve encoded plasmid in combination with the plasmid encoding OX40 or its fragment administration is only produce an enhanced immune response possibly, but it is not sufficient to support the broadly claimed subject matter as vaccine for any pathogen infection or cancer development. In addition, no support for any fragment of OX can be used as an adjuvant for producing same OX activity.

30. The level of skill in the art is very high for developing a vaccine for any or all pathogenic infection or cancer development. Applicants do not provide the sufficient evidence to support the broadly claimed subject matter cited in the claims.

31. Given the above analysis of the factors which the courts have determined are critical in asserting whether a claimed invention is enabled, it must be considered that the skilled artisan would have to conduct undue and excessive experimentation in order to practice the claimed invention.

Claim Rejections - 35 USC § 112

32. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

33. Claims 22, 23, 24, 28-29 are vague and confusing how one or more proteins encodes OX40, because OX40 is one protein. Please explain.

34. Informality issues:

Claim Objections

35. Claim 1 is objected to because of the following informalities: the plural forms of separate nucleic acids cited in the lines 11-12 should be in a singular form, i.e. nucleic acid sequence.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BAO LI whose telephone number is (571)272-0904. The examiner can normally be reached on 6:30 am to 3:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mondesi Robert can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Bao Qun Li/

Examiner, Art Unit 1648

1.